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RESEARCH**

**APPLICATION NUMBER: 17-892/S-034**

**APPROVABLE LETTER**



NDA 17-892/S-034

Pharmacia & UpJohn  
Attention: Roma Thomas  
Regulatory Manager  
7000 Portage Road  
Kalamazoo, MI 49001-0199

Dear Ms. Thomas:

Please refer to your supplemental new drug application dated August 20, received August 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Halcion (triazolam) 0.125 mg and 0.25 mg Tablets.

This "Prior Approval" supplemental new drug application proposes revisions to the **CLINICAL PHARMACOLOGY** section and the addition of a new section under **PRECAUTIONS** entitled **Geriatric Use** to add additional information on geriatric use and to comply with a Federal Register notice dated August 27, 1997.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to make the following revisions to labeling (strike through font denotes deletions and double underline font denotes additions to your proposed labeling):

Under **CLINICAL PHARMACOLOGY**

In a study of elderly, (62 - 83 years old), versus younger subjects, (21 - 41 years old), who received Halcion at the same dose levels, (0.125 mg and 0.25 mg), the elderly experienced both greater sedation and impairment of psychomotor performance. These effects resulted largely from \_\_\_\_\_ higher plasma concentrations of triazolam in the elderly: \_\_\_\_\_

Under **PRECAUTIONS-Geriatric Use**

[Your proposed addition of this subsection is acceptable.]

Under **DOSAGE AND ADMINISTRATION**

[We are requesting the following minor modifications to labeling.]

The recommended dose for most adults is 0.25 mg before retiring.... In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg - to 0.25 mg. Therapy should be initiated at 0.125 mg in these groups and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

The essence of the proposed statements is that the elderly are more susceptible to dose related adverse effects, specifically sedation, psychomotor coordination and other effects, and that this increased susceptibility is due to higher concentrations \_\_\_\_\_. This is based upon the article published in the New England Journal of Medicine (NEJM) and submitted to support your proposed labeling revisions. However, the claim \_\_\_\_\_ is not well supported by this article. For the higher concentrations, mechanisms other than \_\_\_\_\_ are more consistent with the data. In addition, the claim \_\_\_\_\_ does not appear to hold up upon critical analysis.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Russell Katz  
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